Challenging the dogma for the resuscitation of traumatic hemorrhagic shock.

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Disclosures

● Consultant
  – US Army Blood Research Program
  – Norwegian Navy Blood Research Program
  – TerumoBCT, Entegrion, Octapharma

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  – Haemonetics, Diapharma

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  – NIH/NHLBI, 5R01HL095470-02
Objectives

● Review trauma epidemiology and transfusion medicine dogma
● Present data that challenges this dogma
● Suggest areas of research needed to improve outcomes for patients in hemorrhagic shock
  – Trauma and non-trauma
Trauma Epidemiology

- Trauma #1 cause of mortality
  - 1-40 years of age

- Hemorrhage most common cause of preventable death

- Hemorrhagic deaths occur very rapidly
  - 6-12 hours from admission

- Majority of preventable deaths occur in the pre-hospital area

US Military Death Distribution
4,596 Combat Deaths (2001-11)

● 90% of combat deaths occur before reaching Role 2
  – PRE-HOSPITAL

● 25% of pre-hospital deaths are preventable
  – 90% of these are due to hemorrhage, mostly truncal

US Military at risk of Bleeding to Death in Iraq / Afghanistan

Numbers to keep in mind:
• 58,831 = dead + wounded
• 53,724 = survivors + potential survivors
• 8,836 transfused, ≈50% MT, avg. 12.3

Frequency of hemorrhagic shock
• 4000 requiring massive transfusion
• 1,300 KIA, died of hemorrhage with survivable injuries

These 5,300 casualties would have been the most likely to benefit from Blood Far Forward.

10% of injured soldiers are at very high risk of death due to hemorrhage.

This at-risk group represents, on average, one soldier per day of war, or 1 out of 15 wounded per day!
Sutton’s Law

● When Willie Sutton, a very successful bank robber, was asked after he was caught
  – “Why did you rob all those banks?”
  – “Because that is where the money is.”

● The most effective way to improve outcomes for patients with traumatic injury is to prevent death from hemorrhage

● We must then prioritize the implementation and study of clinical practices that can prevent death from hemorrhage, especially in the pre-hospital setting.
Remote Damage Control Resuscitation

● Damage Control Resuscitation principles applied in pre-hospital setting
  – Hypotensive resuscitation
  – Rapid surgical control
  – Minimize crystalloids
  – Hemostatic resuscitation with whole blood or 1:1:1 unit ratio of blood components
  – Appropriate use of hemostatic adjuncts
  – Fresh RBCs if available
  – Address acidosis, hypothermia, hypocalcemia, hypomagnesemia

● RDCR alters DCR concepts when appropriate
  – Example: Hypotensive Resuscitation for prolonged transports
Mission Statement: To reduce the risk of pre-hospital death from hemorrhagic shock secondary to traumatic injuries through research, training and education.

Leadership Structure

- Co-Chairs: 2 members
- Executive Steering Committee: 12 members
  - 6/6 US and non-US
  - 6/6 Military and civilian
  - Multidisciplinary and Multinational
    - Trauma and Transfusion leaders from Norway, US, UK, Israel, Netherlands, Germany, France

211 members from 18 countries
Mission
To reduce the risk of death from traumatic hemorrhagic shock prior to admission at a trauma center.

"Blessed are the young who can give back life with their blood."
Advocates for training, education and research
- Lyophylized plasma
- Tranexamic acid mechanisms and safety
- Pre-hospital care documentation and registry development
- Hemostatic dressings
- Point of care coagulation and shock monitoring
- Optimal TBI management with hemorrhagic shock
- Safety of hypotensive resuscitation
- Hypothermia prevention
Transfusion Medicine

- Evolved from the need to treat combat casualties in WWI
- Over time some practices and standards have developed into “Dogma”
- Many influences for Transfusion Medicine Dogma
  - Economics
  - Conflict of interest
- Dogma needs to continually be questioned or challenged to accelerate change and advancement in medicine.
Transfusion Medicine

Dogma that needs Re-evaluation

● Blood components therapy is as effective or superior to whole blood for patients with severe hemorrhage

● Whole blood is not safe
  – WBCs within whole blood cannot be filtered and are immunologically active

● Whole blood MUST be ABO specific
  – Low titer group O whole blood will cause severe adverse reactions
Transfusion Medicine
Dogma that needs Re-evaluation

- Platelets are more functional when stored at 22°C
  - Based upon definition of function
  - Whole blood at 4°C should not be stored for more than 48 hours

- RBCs stored for 42-56 days are effective at delivering oxygen and treating shock
  - Long history of use and they “appear to work”
  - If RBC storage age was limited to fresher RBCs there would be increased waste and potential for lack of RBC availability
Change from Whole Blood to Component Therapy

- 70-80’s shift from whole blood to individual blood components
  - Technology made it possible
  - Concept was to provide specific components for single deficiencies
    - Anemia – RBCs
    - Thrombocytopenia – platelets
    - Coagulopathy – plasma
  - No clinical data to support equivalence
Trauma Patients with Massive Bleeding

- Patients don’t have a specific deficit
- Trauma resuscitation dogma became
  - Give fluids and RBCs first since this will treat the shock
  - Wait for documented coagulopathy
    - Plasma
  - Wait for documented thrombocytopenia
    - Platelets
Whole Blood Availability Became Restricted

- Inability to leukoreduce and maintain platelets
- Hard to maintain inventory of ABO specific whole blood
- Concept that platelets at 4C are non-functional
Questioned Dogma: Component Therapy is Equivalent or Superior to Whole Blood for Hemorrhagic Shock

- Previously thought that patients with massive hemorrhage will benefit from use of individual blood components to treat specific deficits
  - Shock is primary problem so give RBCs to reverse shock
    - RBCs at storage age transfused suboptimal for O2 delivery
    - Hemostasis supported by 30% of coagulation factors
      - Plasma can be given later in resuscitation
      - THIS IS FALSE!
  - Platelets are not required early in resuscitation of bleeding patients
    - Can be given late once count is low
    - THIS IS FALSE!
Dogma Challenge #1

- Whole blood is **superior** to blood components the way components are distributed

- Whole blood is **more practical** to give in the pre-hospital setting for massive bleeding
  - Hospital setting too
Rationale for Whole Blood Superiority to Components

- More concentrated product vs. reconstitution of whole blood with components in 1:1:1 unit ratio
- Fresh product
  - Improved efficacy
- Avoids storage lesion
  - Improved safety
  - Improves efficacy
Component Therapy:
1U PRBC + 1U PLT + 1U FFP + 1 U cryo
680 mL
• Hct 29%
• Plt 80K
• Coag factors 65% of initial concentration

Whole Blood:
500 mL
• Hct: 38-50%
• Plt: 150-400K
• Coag concentration 100%

### Component Therapy per Unit:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount (mL)</th>
<th>Total (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 x RBC (AS-5)</td>
<td>6 x 120 ml</td>
<td>720 ml</td>
</tr>
<tr>
<td>6 x FFP</td>
<td>6 x 50 ml</td>
<td>300 ml</td>
</tr>
<tr>
<td>1 x aPLT</td>
<td>1 x 35 ml</td>
<td>35 ml</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1055 ml</strong></td>
</tr>
</tbody>
</table>

### Whole Blood per Unit:

- **Total:** 378 ml

There is 3 times the volume of anticoagulant and additives with reconstituted whole blood from components compared to whole blood.

Spinella PC, J Trauma. 2009;66:S69-76
Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children

CS Manno, KW Hedberg, HC Kim, GR Bunin, S Nicolson, D Jobes, E Schwartz and WI Norwood
Manno - Methods

- Prospective double-blinded study
  - 161 children requiring cardiac surgery

- Patients were randomized to
  - Warm FWB (< 6 hours at 20 degrees C)
  - Cold FWB (24 - 48 hours at 4-6 C)
  - Reconstituted whole blood (1:1:1)
    - (RBCs ≤ 5 days of storage, FFP, and platelets).

Table 2. Patient Characteristics for the Three Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (VFWB)</th>
<th>Group II (24-48 h Old)</th>
<th>Group III (Reconstituted Whole Blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>52</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Ages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± S.E. (y)</td>
<td>2.8 ± 0.4</td>
<td>3.9 ± 0.6</td>
<td>3.8 ± 0.8*</td>
</tr>
<tr>
<td>Range</td>
<td>(0-8.2)</td>
<td>(0-19)</td>
<td>(0-20)</td>
</tr>
<tr>
<td>No. &lt; 2 y</td>
<td>27</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>No. &gt; 2 y</td>
<td>25</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Surgical difficulty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple (no. subjects)</td>
<td>11</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Complex</td>
<td>29</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Mean time ± SE on bypass (min)</td>
<td>86.8 ± 6.2</td>
<td>86.1 ± 5.8</td>
<td>84.2 ± 5.1†</td>
</tr>
<tr>
<td>Mean time ± SE of circulatory arrest</td>
<td>38.1 ± 4.3</td>
<td>43.6 ± 4.6</td>
<td>37.2 ± 3.7‡</td>
</tr>
<tr>
<td>Mean volume blood given (Cm³/kg) in 24 h</td>
<td>72.3 ± 9.9</td>
<td>75.5 ± 7.8</td>
<td>97.4 ± 9.6§</td>
</tr>
<tr>
<td>No. of subjects with circulatory arrest</td>
<td>41</td>
<td>42</td>
<td>39</td>
</tr>
</tbody>
</table>

*P = .37.
†P = .94.
‡P = .51.
§P = .11.
## Manno - Results

<table>
<thead>
<tr>
<th></th>
<th>Warm FWB</th>
<th>Cold FWB</th>
<th>Recon Blood</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24 hr blood loss (ml/kg)</strong></td>
<td>50.9 (±9)</td>
<td>44.8 (±6)</td>
<td>74.2 (±9)</td>
<td>0.03∞</td>
</tr>
<tr>
<td><strong>24 hr blood loss (ml/kg)</strong> &lt; 2 yrs</td>
<td>52.3 (±11)</td>
<td>51.7 (±7.4)</td>
<td>96.2 (±11)</td>
<td>0.001 §</td>
</tr>
<tr>
<td><strong>PTT (30 min)</strong></td>
<td>38.2 (±1.1)</td>
<td>39.7 (±3.4)</td>
<td>43.3 (±1.8)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Fibrinogen (mg/dl)</strong></td>
<td>202 (±5.4)</td>
<td>195 (±5.6)</td>
<td>184 (±4.8)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>PLT aggregation (30 min)</strong></td>
<td></td>
<td></td>
<td>most reduced</td>
<td>0.02</td>
</tr>
</tbody>
</table>

∞ cold vs recon  
§ warm and cold vs recon

Fresh Whole Blood versus Reconstituted Blood for Pump Priming in Heart Surgery in Infants

Mou - Methods

- RCT of cold stored FWB to reconstituted blood (RBCs and FFP) in the pump prime
- 200 pediatric cardiac surgery patients < 1 year of age.
- No FWB post-operatively in the ICU where outcomes were measured.
- The primary outcome of this study was a composite score for survival and ICU LOS.

Mou - Results

- No difference in groups compared
  - Age, sex
  - Illness severity score, diagnoses
  - CPB or CA times

- Post-op no difference in
  - Composite outcome score between study groups
    - Primary study outcome
  - Transfusion requirement
  - Chest tube output

Mou – Results/Discussion

- Secondary outcome
  - Increased ICU LOS in FWB group
    - ICU LOS - 97 hrs vs. 70 hrs, (p=0.04)
- Not adjusted for potential confounders
  - Use of extracorporeal membrane oxygenation
  - ECMO 6 vs. 2 in FWB vs. Recon blood group

Warm Fresh Whole Blood Is Independently Associated With Improved Survival for Patients With Combat-Related Traumatic Injuries

Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, and John B. Holcomb, MD

968 patients in database

614 excluded

354 (37%) patients included

254 (72%) CT patients

100 (28%) WFWB patients

530 neither WB/PLT

84 both WB/PLT

30% total blood volume = WFWB
Survival

Days

Log rank test, p= 0.002

Spinella PC, J Trauma. 2009;66:S69-76
### Multi-variate Logistic Regression for 30 day survival – Patient study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFWB group*</td>
<td>15.4 (2.3 – 106)</td>
<td>0.005</td>
</tr>
<tr>
<td>Plasma:RBC ratio</td>
<td>10.3 (2.3 - 45.)</td>
<td>0.002</td>
</tr>
<tr>
<td>ISS</td>
<td>0.94 (0.91 - 0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>GCS eyes (normal)</td>
<td>3.91 (1.5 - 10.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Base deficit</td>
<td>0.88 (0.82 – 0.95)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Referent group were CT patients
AUC (95% CI) = 0.9 (0.85-0.95)
## Multi-variate Logistic Regression for 30 day survival – individual blood product amounts

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95.0% C.I.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFWB (U)</td>
<td>2.15 (1.21-3.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>Plasma (U)</td>
<td>1.09 (1.02-1.18)</td>
<td>0.019</td>
</tr>
<tr>
<td>RBC (U)</td>
<td>0.91 (0.85-0.97)</td>
<td>0.003</td>
</tr>
<tr>
<td>Base Deficit</td>
<td>0.91 (0.84-0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>GCS eyes (normal)</td>
<td>3.8 (1.4-10.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>ISS</td>
<td>0.94 (0.91-0.98)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

\[
AUC (95\% CI) = 0.9 (0.86 – 0.95)
\]

Spinella PC, J Trauma. 2009;66:S69-76
Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients

TRANSFUSION 2011;51:242-252.

US and Foreign Nationals – Massive transfusion only
- 40% are US patients
- High rate of censoring prior to 30 day survival
  - 245/369 (66%) still available at 30 days
- Different use of personal protective gear
- 20% of blood is FWB in that group

Fig. 2. Unadjusted Kaplan-Meier survival curves comparing FWB to aPLT groups.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Logistic regression for mortality at 24 hr*</th>
<th>Cox regression for mortality at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>aPLT group†</td>
<td>3.38 (0.96-11.87)</td>
<td>1.38 (0.77-2.47)</td>
</tr>
<tr>
<td>US nationality</td>
<td>0.35 (0.12-1.02)</td>
<td>0.33 (0.18-0.59)</td>
</tr>
<tr>
<td>TISS</td>
<td>0.57 (0.44-0.74)</td>
<td>0.71 (0.64-0.79)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>0.69 (0.48-1.01)</td>
<td>1.00 (0.84-1.21)</td>
</tr>
<tr>
<td>PLT count (1 x 10⁹/L)</td>
<td>1.00 (0.99-1.01)</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>INR</td>
<td>1.45 (0.97-2.16)</td>
<td>1.21 (1.01-1.45)</td>
</tr>
<tr>
<td>Base deficit (mEq/L)</td>
<td>1.05 (0.98-1.13)</td>
<td>1.02 (0.99-1.06)</td>
</tr>
<tr>
<td>Total RBC units‡</td>
<td>1.06 (1.02-1.11)</td>
<td>1.02 (0.99-1.04)</td>
</tr>
<tr>
<td>Plasma ratio (%)§</td>
<td>0.94 (0.92-0.97)</td>
<td>0.99 (0.98-0.999)</td>
</tr>
<tr>
<td>rFVIIa usage</td>
<td>0.86 (0.29-2.57)</td>
<td>1.05 (0.61-1.83)</td>
</tr>
</tbody>
</table>

**Note:**

* OR: Odds Ratio

† aPLT group is significantly associated with mortality at 24 hours.

‡ Total RBC units are significantly associated with mortality at 30 days.
Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets

TRANSFUSION 2013;53:107S-113S.

Nessen Whole Blood at FST

Methods

● Retrospective study of prospectively collected data
● 6 FST from 2005-2010
● Included patients transfused any blood products
● FWB group
  – RBC, plasma, FWB
● No FWB group
  – RBC, plasma
● Propensity analysis used to adjust for differences between patients transfused FWB or not
● In hospital mortality was primary outcome
Nessen Whole Blood at FST Results

- 488 patients transfused any blood products

<table>
<thead>
<tr>
<th></th>
<th>No FWB (n = 394)</th>
<th>FWB (n = 94)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.6 ± 11.5; 25 (20, 30); 371</td>
<td>28.1 ± 9.7; 25 (22, 30); 81</td>
<td>0.08</td>
</tr>
<tr>
<td>US and/or coalition</td>
<td>53 (13.5)</td>
<td>14 (14.9)</td>
<td>0.715</td>
</tr>
<tr>
<td>Non-US and/or coalition</td>
<td>341 (86.5)</td>
<td>80 (85.1)</td>
<td>0.715</td>
</tr>
<tr>
<td>Male sex</td>
<td>375 (95.2)</td>
<td>90 (95.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>GCS</td>
<td>13.8 ± 2.7; 15 (14, 15); 394</td>
<td>13.2 ± 3.4; 15 (14, 15); 93</td>
<td>0.11</td>
</tr>
<tr>
<td>ISS</td>
<td>19.6 ± 9.3; 16.5 (16, 25); 394</td>
<td>22.4 ± 8.9; 20 (16, 26); 94</td>
<td>0.008</td>
</tr>
<tr>
<td>Arrival SBP (mmHg)</td>
<td>110.5 ± 27.1; 110 (95, 128); 388</td>
<td>99.9 ± 30.1; 97 (80, 123); 94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrival RR</td>
<td>22 ± 8.2; 21 (16, 26); 383</td>
<td>25.2 ± 9.7; 25 (18, 30); 94</td>
<td>0.005</td>
</tr>
<tr>
<td>Arrival temperature (°C)</td>
<td>36.4 ± 0.8; 36.6 (36.2, 37.0); 373</td>
<td>36.1 ± 1.2; 36.2 (35.6, 36.8); 83</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Nessen Whole Blood at FST Results

- Mortality
  - No FWB, 8.8%
  - FWB, 5.3%

### TABLE 6. Propensity score used as continuous variable in logistic regression predicting effect of FWB on death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWB use</td>
<td>0.096</td>
<td>0.02, 0.53</td>
<td>0.008</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>1.07</td>
<td>1.03, 1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>0.72</td>
<td>0.65, 0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Propensity score</td>
<td>9.72</td>
<td>1.45, 64.97</td>
<td>0.019</td>
</tr>
</tbody>
</table>
Effect of blood transfusion on survival among children in a Kenyan hospital

Eve M. Lackritz Carlos C. Campbell
Trenton K. Ruebush II Allen W. Hightower
Wataka Wakube Richard W. Steketee Joab B. O. Were
Pediatric Kenya Whole Blood Study

Methods

● Prospective Observational Study

● Children < 12 years of age with whole blood transfusion

● Whole blood collected from family members
  – No mention of storage temperature or duration

● Compared mortality between transfused and not transfused patients
Pediatric Kenya Whole Blood Study Results

Whole blood associated with reduced mortality

- If Hb < 3.9 g/dl and transfused on Day 1
  • OR 0.3, (95% CI, 0.14-0.61)
- If Hb < 3.9 g/dl and transfused on Day 2
  • OR 0.37, (95% CI, 0.14-1.0)
- If Hb < 4.7 g/dl and respiratory distress
  • OR 0.19, (95% CI 0.09-0.41)
Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time

--- = CON 22; ↔ = CON 4; → = PRT 22; ↔ ↔ = PRT 4.
Components vs. Whole Blood Summary

- Most **whole blood** data indicates improved outcomes
  - Including an RCT in children
- Dogma that components are equivalent or superior is NOT SUPPORTED by literature.
- Definitely not supported by experience.
- Platelet function in whole blood maintained to at least 10 days at 4C.
Questioned Dogma #2: Whole Blood Must be ABO Specific

- If whole blood is not ABO specific
  - High risk of hemolysis and adverse effects
Current Policies

- AABB
  - Whole blood must be type specific

- DoD
  - Whole blood must be type specific
Dogma Challenge #2

- Low titer Type O whole blood is actually safer than ABO specific whole blood.

- This would allow for increased availability
  - Inventory needed to stock just low titer Type O
LOW TITER GROUP O WHOLE BLOOD IN EMERGENCY SITUATIONS

Conclusion: Low titer Group O is preferred alternative for emergency transfusions where safe ABO identical transfusions cannot be ensured.
ABO Group Background

- Lethal potential of incompatible transfusion determined by number of RBCs hemolyzed
  - Donor or recipient RBCs

- Risk for severe hemolytic reaction
  - ABO incompatible RBCs >>>> ABO incompatible plasma
ABO Group Background

- Acute hemolytic reaction
  - Major ABO incompatibility
  - Donor RBCs transfused to recipient with non-compatible ABO Abs
  - Can be avoided by transfusing Type O RBCs

- Transfusion of Type O whole blood offers same protection against an acute hemolytic reaction than Type O RBCs
● Minor ABO incompatibility
  – Transfusion of non-compatible ABO Abs to recipient RBCs
  – Clinical consequences are MINOR and frequently subclinical

● Platelets are not ABO specific when transfused
  – Plasma in platelets unit is similar to amount in plasma or whole blood unit
    • 200-300 ml
  – 1:10,000 risk of mild clinical hemolytic reactions
ABO Paradox

● Why require whole blood transfusions to be type specific to protect against minor ABO incompatibility while permitting transfusion of ABO incompatible platelets?
  – Similar volume of plasma in both products

● Use of Group O whole blood
  – Similar risk of Group O RBCs
  – Similar risk of Platelet Transfusions
Group O Whole Blood Experience

● WW I
  – 15 cases reported, all mild reactions
  – High ABO titers measured from donors, IgM > 256

● WW II
  – Practically all blood transfused was Group O whole blood
  – Of 256 ABO incompatible Group O transfusions, 3 mild hemolytic reactions reported
    • All ABO IgM titers > 500
  – One report of severe reaction from ABO IgM titer of 8000
    • Army policy that ABO titer must be < 250 for Group O whole blood to be universal donor.
Group O Whole Blood Experience

- Korea
  - 400,000 low titer Group O whole blood transfusions with no severe hemolytic reactions when low titer defined as < 250

- Vietnam
  - 230,300 whole blood transfusions, 1967-1969
    • 1 severe hemolytic transfusion reaction
    • High titer (> 256) Group O whole blood used accidentally
Current International Policy

● Low titer Group O whole blood permitted for military use
  – UK, Norway, Sweden
  – UK testing indicates 3-10% Group O donors are high anti A/B titer

● Conditional military use
  – Australia, France

● Do not permit low titer Group O whole blood
  – US
    • Still happens which is more dangerous
      – No training or teaching
      – Will be kept quiet and not reviewed
Definition of Low Titer

No standard international definition
- US Korean War and Vietnam standard
  - IgM < 250
- Norwegian and UK definitions
  - IgM < 100 or IgG < 400
Risk Comparison

- Plasma Incompatible ABO from UK SHOT database for platelet transfusions
  - 1:120,000 risk of **MODERATE** hemolytic reaction

- Type specific ABO blood products
  - 1:80,000 risk of **SEVERE** hemolytic reaction
    - Human error
    - Risk is elevated in austere environments!
<table>
<thead>
<tr>
<th>Benefits</th>
<th>ABO group–specific WB</th>
<th>Low-Titer Group O WB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. ABO compatibility of RBCs and plasma after typing of donor and recipient or full crossmatch</td>
<td>1. ABO compatibility of RBCs with all major blood groups</td>
</tr>
<tr>
<td></td>
<td>2. Few minor ABO incompatibility transfusion reactions</td>
<td>2. Few minor ABO incompatibility transfusion reactions</td>
</tr>
<tr>
<td></td>
<td>3. No need to ABO group or crossmatch the recipient if immediate transfusion is crucial for survival</td>
<td>3. No need to ABO group or crossmatch the recipient if immediate transfusion is crucial for survival</td>
</tr>
<tr>
<td></td>
<td>4. Readily available due to high frequency of low-titer group O donors (approximately 95%–70% of group O donors if IgG &lt;400, IgM &lt;100)</td>
<td>4. Readily available due to high frequency of low-titer group O donors (approximately 95%–70% of group O donors if IgG &lt;400, IgM &lt;100)</td>
</tr>
<tr>
<td></td>
<td>5. Safer in chaotic and remote situations (no risk of mismatched RBC transfusion due to clerical error)</td>
<td>5. Safer in chaotic and remote situations (no risk of mismatched RBC transfusion due to clerical error)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk or burden</th>
<th>ABO group–specific WB</th>
<th>Low-Titer Group O WB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Increased risk of a hemolytic reaction due to major ABO incompatibility*</td>
<td>1. Risk of mild to moderate hemolytic reactions due to minor ABO incompatibility. No WB data available. Data from titrated donors platelet transfusions estimated 1:120,000†</td>
<td></td>
</tr>
<tr>
<td>2. Increased risk of underresuscitation due to limited availability of some ABO group–specific donors</td>
<td>2. Risk of severe hemolytic reaction if anti-A/B titer not accurately identified (clerical error)‡</td>
<td></td>
</tr>
<tr>
<td>3. Need to ABO group donor and recipient</td>
<td>3. Need to titer group O donors</td>
<td></td>
</tr>
<tr>
<td>4. Excludes 5%–30% of group O donors§ (depending on critical titer for anti-A/B used)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In civilian hospital settings: wrong blood 1:15,000; ABO-incompatible 1:40,000; HTR 1:80,000 (52).
†Estimated from UK SHOT 2011–2012 based on estimated 20% out-of-group platelet transfusions (13).
‡No fatal reactions reported from Korea where approximately 400,000 group O–labeled (high and low titer) WB units were transfused.
§NHS Blood and Transplant (26).
Summary

● No data to support current policy that whole blood must be ABO specific

● Data indicates that Low titer Type O whole blood is safer when human error included

● **Current MEDCOM policies regarding type specific whole blood require immediate review and reconsideration**

● Definition of low titer must be established.
Questioned Dogma #3: Whole blood is not safe because it can’t be leukoreduced

- Old leukoreduction filters also removed platelets
- Whole blood in past was not leukoreduced because maintaining platelets was essential
- Concern that the WBCs remaining in whole blood could be immunomodulatory
Challenge #3

- Whole blood can be leukoreduced and platelets remain intact.
- Imuflex filter is FDA approved leukoreduction filter for whole blood that is platelet sparing.
- Currently the ARC uses this filter for whole blood sent to Children’s Hospital of Philadelphia.
- In fact 15% of children’s hospitals surveyed use fresh whole blood licensed by FDA.
  - Use of imuflex filter at these sites is unknown.
The LR Express
The first direct line to leukocytes reduced platelets

ALL ABOARD for the first in-line, single-filter system that yields leukocytes reduced (LR) whole blood for the production of red blood cells (RBCs), platelets, and plasma.

IMUFLEX® WB-SP
BLOOD BAG SYSTEM

The LR Express

TERUMO TRANSFUSION PRODUCTS
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood</td>
<td></td>
<td>n = 56</td>
<td>n = 22</td>
<td>n = 37</td>
</tr>
<tr>
<td>RBC Mass (Hematocrit) Recovery</td>
<td>≥ 85%</td>
<td>91% ± 3%</td>
<td>90% ± 3%</td>
<td>89% ± 3%</td>
</tr>
<tr>
<td>Residual WBC</td>
<td>&lt; 5.0 x 10^6 cells/unit</td>
<td>&lt; 1.62 ± 1.08 x 10^5</td>
<td>&lt; 3.78 ± 1.17 x 10^4</td>
<td>&lt; 5.24 ± 2.98 x 10^4</td>
</tr>
<tr>
<td>AS-5 Red Blood Cells</td>
<td></td>
<td>n = 0</td>
<td>n = 22</td>
<td>n = 37</td>
</tr>
<tr>
<td>Residual WBC</td>
<td>&lt; 5.0 x 10^6 cells/unit</td>
<td>Not Tested</td>
<td>&lt; 2.94 ± 1.84 x 10^4</td>
<td>&lt; 3.02 ± 1.11 x 10^4</td>
</tr>
<tr>
<td>Platelet</td>
<td></td>
<td>n = 49</td>
<td>n = 20</td>
<td>n = 37</td>
</tr>
<tr>
<td>PLT Count (at Day 1)</td>
<td>≥ 5.5 x 10^10 cells/unit</td>
<td>8.07 ± 2.25 x 10^10</td>
<td>7.31 ± 2.04 x 10^10</td>
<td>8.90 ± 1.74 x 10^10</td>
</tr>
<tr>
<td>WBC Content (Day 1)</td>
<td>&lt; 8.3 x 10^5 cells/unit</td>
<td>&lt; 1.68 ± 1.32 x 10^4</td>
<td>&lt; 5.73 ± 2.53 x 10^3</td>
<td>&lt; 5.10 ± 1.75 x 10^3</td>
</tr>
<tr>
<td>pH (at Day 5/6)</td>
<td>≥ 6.2</td>
<td>7.26 ± 0.24</td>
<td>7.19 ± 0.31</td>
<td>7.35 ± 0.14 (n = 36)</td>
</tr>
</tbody>
</table>
Norwegian Imuflex SP Data

- Platelet function remains within normal limits
  - TEG testing
  - Multiplate whole blood aggregometry

- When pushed through pressure bag in < 10min
  - Platelet function remains within normal limits
    - Despite reduced number of platelets
  - Leukoreduction is 99%
    - Does not meet FDA criteria
    - Still 99% leukoreduction

- All of this data in process of submission for publication
Imuflex SP Filter Summary

- FDA licensed platelet sparing leukoreduction filter exists
- Clinically made available by ARC in Philadelphia
- Can be used to improve safety profile of whole blood
- Platelet function is not altered by filter
Whole Blood Education and Training

- Not emphasized or taught routinely to Medics
- Lack of education and training can increase adverse events and inappropriate use
EMERGENCY WHOLE-BLOOD USE IN THE FIELD: A SIMPLIFIED PROTOCOL FOR COLLECTION AND TRANSFUSION

Geir Strandenes,*,† Marc De Pasquale,‡ Andrew P. Cap,§ Tor A. Hervig,†
Einar K. Kristoffersen,† Matthew Hickey,‖ Christopher Cordova,‖‖ Olle Berseus,**
Håkon S. Eliassen,† Logan Fisher,‖‖‖ Steve Williams,‖‖‖‖ and Philip C. Spinella§§§

*Norwegian Naval Special Operation Commando; and; †Department of Immunology and Transfusion Medicine, Haukeland University Hospital, and Institute of Clinical Science, University of Bergen, Bergen, Norway; ‡Deployment Medicine International, Gig Harbor, Washington; §US Army Institute of Surgical Research, Fort Sam Houston, Texas; ‖Naval Special Warfare Command, San Diego, California; ‖‖Specialist Corps, US Army, Keller Army Community Hospital, West Point, New York; **Department of Transfusion Medicine, Örebro University Hospital, Örebro, Sweden; ‖‖‖NSWDG US Navy, Virginia Beach, Virginia; ‖‖‖‖Medical Operations Royal Caribbean Cruises Ltd.; and §§§Department of Pediatrics, Division of Critical Care, Washington University in St. Louis, St. Louis, Missouri
Provider Letter of Understanding for Untested Emergency Whole Blood Units

I understand that these Emergency Whole Blood Units have not had complete Rapid Testing prior to transfusion and transfusion of these units may result in an increased risk of unintended disease and/or transfusion reactions. I accept full responsibility for the units and the consequences that may follow transfusion.

Print       Sign       Date

_________________________  ___________________________  __________
Provider

Form 150b
Form 150-B

- Coercive
- Not applied consistently
  - Apheresis platelets also not FDA approved
- Should not be required to be signed
ORIGINAL ARTICLE

TRANSFUSION

Donor performance of combat readiness skills of special forces soldiers are maintained immediately after whole blood donation

A study to support the development of a prehospital fresh whole blood transfusion program

Geir Strandenes, Håkon Skogrand, Philip C. Spinella, Tor Hervig, and Erling B. Rein

Transfusion. 2013 Mar;53(3):526-30
Fluid Resuscitation for Hemorrhagic Shock in Tactical Combat Casualty Care

TCCC Guidelines Change 14-01

28 June 2014

Conclusions

1. The preferred fluids for resuscitation of casualties in hemorrhagic shock, in descending order of preference, are:
   - Whole blood
   - 1:1:1 plasma, RBCs, and platelets
   - 1:1 plasma and RBCs
   - Reconstituted dried plasma, liquid plasma, or thawed plasma alone or RBCs alone
   - Hextend
   - Lactated Ringers or Plasma-Lyte A
When somebody says whole blood just can’t be done……..

- Royal Caribbean Cruise Liners
  - 100,000 guests plus 37,000 crew at sea in 34 different ships each day
  - Many guests, elderly, overweight, over-eating and on anticoagulants
    - High risk of GI bleeding
  - Often vessels 24 hours from any port
  - Operationalized a Fresh Whole Blood Transfusion Program
    - Recurrent training and education of 250 medical personnel
    - Screening questionnaires, rapid ABO typing and infectious disease testing
- 40 months there were 40 whole blood emergent transfusions
  - 1-6 Units per patient
  - One allergic reaction, no infectious complications
Questioned Dogma #4: Platelet are more functional when stored at 22C

- In late 60’s to early 70’s known that
  - Platelets at 22C circulated longer but were not hemostatically active
  - Platelets at 4C were hemostatically active but removed from circulation faster

- Definition of function
  - Circulation time of hemostatic activity

- Primary customer of platelets are oncology
  - Circulation time prioritized

- Low enthusiasm for double inventory
  - Warm and cold platelets
Dogma Challenge #4

- Platelets stored at 4C are functional for hemostasis and should be made available for severe bleeding.

- Whole blood derived platelets at 4C - licensed by FDA
  - Collection bag was licensed at 4C decades ago by FDA
  - Can’t get them anyway because blood collection agencies do not think they are functional

- Apheresis Platelets at 4C - not licensed by FDA
  - Collection bag never tested at 4C
Studies of Platelet Concentrates Stored at 22 C and 4 C


From the Milwaukee Blood Center, Inc., and Department of Medicine,
Medical College of Wisconsin, Milwaukee, Wisconsin
Fig. 2. Mean maximum aggregation (per cent of maximum possible O.D. change) with $2 \times 10^{-5}$ M ADP. On days one to five, differences were significant ($p < .001$).
Fig. 4. Platelet increment one hour following transfusion of platelets to thrombocytopenic patients (± 1 standard error of the mean) (S.E.M.). Differences of the means at two and three days are significant (p < .01). Calculation of “expected rise” is given in “methods.”
Impact of the Duration of Platelet Storage in Critically Ill Trauma Patients

(Kenji Inaba, MD, FRCSC, FACS, Bernardino C. Branco, MD, Peter Rhee, MD, MPH, FACS, Lorne H. Blackbourne, MD, FACS, John B. Holcomb, MD, FACS, Philip C. Spinella, MD, FACS, Ira Shulman, MD, Janice Nelson, MD, and Demetrios Demetriades, MD, PhD, FACS)
HEMOSTATIC FUNCTION OF APHERESIS PLATELETS STORED AT 4°C AND 22°C

Kristin M. Reddoch,* Heather F. Pidcock,† Robbie K. Montgomery,†
Chriselda G. Fedyk,† James K. Aden,† Anand K. Ramasubramanian,*
and Andrew P. Cap†

*Department of Biomedical Engineering, The University of Texas at San Antonio, San Antonio, Texas;
and †US Army Institute of Surgical Research, Fort Sam Houston, Texas

Shock. 2014 May;41 Suppl 1:54-61.
Platelet Activation Markers

A: CD62P (% Total)
B: Lactadherin % Total
C: CD40L (% Total)

Platelet Aggregation Results

A: ADP
B: Collagen
C: TRAP
Fig. 2. Measurement of clot properties by TEG. A, R time. B, K time. C, α Angle. D, Maximum amplitude. E, Percent lysis after 30 minutes. Treatment conditions are represented as follows: RT = ■; 4°C = ○; 4°C + AG = △. Data are represented as mean ± SEM. Differences from baseline (*) and between treatment groups (†) are shown if results from both the one-way ANOVA for repeated measures and the post hoc Bonferroni test comparisons are significant (P < 0.05).
Refrigerated Platelets Respond to Physiologic Inhibitors, Evidence That Cold-Induced Activation Is Unlikely to Result in Disseminated Intravascular Coagulation

Authors: KM Reddoch, HF Pidcoke, AK Ramasubramanian, and AP Cap

Figure 1. Aggregation response of stored platelets to 20 uM ADP and 10 ug/ml collagen before and after addition of physiologic inhibitors. Data are means ± SEM for n=4 donors. Difference from fresh baseline (p<0.05) is denoted by *; ns represents p≥0.05 between sample groups treated with the same inhibitor.
Conclusions

- Response to aggregation, a marker of platelet function, was higher in 4C-stored platelets compared to conventional RT, consistent with better preservation of platelet function.

- Conversely, the 4C response to inhibition was similar to fresh, suggesting that 4C platelets remain under physiologic controls and are unlikely to cause DIC *in vivo*.

- The cGMP and cAMP data further suggests that the 4C inhibitory machinery is preserved.
To mimic *in-vivo* conditions, adhesive response in a microfluidic environment under physiologic high-shear flow.

Samples were perfused through the collagen-coated wells at an arterial shear rate of 720s\(^{-1}\), and compared to bovine serum album (BSA)-coated channels as a control to assess nonspecific binding.

A fluorescence microscope acquired images every 30 sec for 6 min.

Data were reported as fluorescence intensity units (FIU) and surface coverage (SC%) measured with Bioflux Montage (MetaMorph) software.
Refrigerated Platelets Are Superior Compared to Standard-of-Care and Respond to Physiologic Control Mechanisms under Microfluidic Flow Conditions

KM Reddco, MA Meledeo, AC Rodriguez, HF Pidcoke, AK Ramasubramanian, and AP Cap

* p<0.05, † p<0.01, and ‡ p<0.001, and § p<0.0001
Conclusions

- These data suggest that 4C platelets, although primed and hemostatically more active, may respond to homeostatic signals *in vivo* and may not pose a risk of promoting unregulated clot formation.

- RT-PLT function is significantly reduced and did not recover activity in this physiologically relevant model.
Bioenergetic Profiling of Platelet Mitochondria during Storage: 4° C Storage Extends Platelet Mitochondrial Function and Viability

James A. Bynum\textsuperscript{1,2}, Michael A. Meledeo\textsuperscript{1}, Todd Getz\textsuperscript{1}, Andrew P. Cap\textsuperscript{1}, Heather F. Pidcoke\textsuperscript{1}

- Mitochondrial respiration, maximal oxygen utilization, and individual mitochondrial complex-dependent respiration were assessed with high-resolution respirometry (O2k, Oroboros).

- Mitochondrial ROS generation in response to: 1). storage condition; 2). stimulation (to assess oxidative burst capacity as a measure of function) was visualized with confocal imaging using a superoxide stain (MitoSOX Red, Life Technologies).
Bioenergetic Profiling of Platelet Mitochondria during Storage: 4°C Storage Extends Platelet Mitochondrial Function and Viability

James A. Bynum¹,², Michael A. Meledeo¹, Todd Getz¹, Andrew P. Cap¹, Heather F. Pidcoke¹

- Mitochondrial respiration was lower in platelets stored at 4°C compared to 22°C on days 3-7 (Day 5= -57%±0.3; P < 0.05), demonstrating that refrigeration slows metabolism.

- Confocal imaging demonstrated that mROS generation was higher in RT-stored platelets compared to 4°C, reflecting mitochondrial damage.

- Mitochondrial burst, as measured with confocal microscopy during de novo mROS generation due to stimulation, was preserved at 4°C.
# Data on Platelet Storage Temperature: Manno - Results

<table>
<thead>
<tr>
<th></th>
<th>Warm FWB</th>
<th>Cold FWB</th>
<th>Recon Blood</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24 hr blood loss (ml/kg)</strong></td>
<td>50.9 (±9)</td>
<td>44.8 (±6)</td>
<td>74.2 (±9)</td>
<td>0.03∞</td>
</tr>
<tr>
<td><strong>24 hr blood loss (ml/kg)</strong></td>
<td>52.3 (±11)</td>
<td>51.7 (±7.4)</td>
<td>96.2 (±11)</td>
<td>0.001 §</td>
</tr>
<tr>
<td><strong>&lt; 2 yrs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PTT (30 min)</strong></td>
<td>38.2 (±1.1)</td>
<td>39.7 (±3.4)</td>
<td>43.3 (±1.8)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Fibrinogen (mg/dl)</strong></td>
<td>202 (±5.4)</td>
<td>195 (±5.6)</td>
<td>184 (±4.8)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>PLT aggregation (30 min)</strong></td>
<td>ADP, epinephrine, collagen</td>
<td>most reduced</td>
<td></td>
<td>0.02</td>
</tr>
</tbody>
</table>

∞ cold vs recon
§ warm and cold vs recon

Additional benefits of Platelet Storage at 4C

● Reduced Cost
  – Improved inventory
    • Doubles storage time at least
    • Improved efficacy will reduce number of units per patient
    • Eliminates bacterial testing

● Reduced Logistical Complexity
  – RBCs and platelets stored at same temperature

● Improved availability far forward
  – Increased shelf life
Questioned Dogma #5: RBCs stored to 42-56 days are efficacious and safe

- Storage solutions have increased from 21 to now 56 days
- Licensing based primarily on survival and recovery
- Presumption that if circulating they are functional
- Safety data focused on infectious risk
Dogma Challenge #5: RBCs of increased storage age have reduced efficacy and safety, which likely effects outcomes

- No data exists demonstrating RBCs of increased age deliver oxygen at cellular level
  - Most evidence demonstrates REDUCED oxygen delivery
- Mounting data that older RBCs increase immune, coagulation and endothelial dysfunction
Trauma Patients are Preferentially Transfused Older RBCs

- **Distribution Policies**
  - RBCs > 35 days shipped to Trauma Centers

- **Allocation Policies**
  - Standard approach is to give the oldest RBC in inventory to minimize waste

- **Sickest patients get the oldest RBCs**

- **Sickest patients have greatest need for RBC product that will increase oxygen delivery**
  - To address the shock and coagulopathy
Evidence of Efficacy of Human RBCs Related to Storage Age

- 1 day RBCs improve microcirculatory perfusion
  - 21 day RBCs do not
- Reduced intestinal pO2 with 35-42 day RBCs
  - Compared to 2-21 day old RBCs
  - Rat model of shock

RBC Safety

- Incr inflammation with old RBC\(^1\)
  - Day 0 vs Day 21
- Incr oxidative injury with old RBC\(^2\)
  - Day 0 vs Day 42
- Incr abnormal apoptosis with old RBC\(^2\)
  - Day 0 vs Day 21
- Incr risk of hypercoagulation\(^3\)
  - Day 4 vs Day 42

1 Zallen G. Shock. 2000. 13;1, p29-33
2 Biffl WL. J Trauma. 2001. 50;3, p426-432
3 Cardo LJ. Trans Apher Science. 2008. 141-147
Impaired RBC Energetics

- Impaired Glycolysis
  - ↓ 2.3 DPG
  - ↑ p50
  - ↓ ATP
  - ↓ Ion Pump
  - ↓ Ion Pump w/ Ion Leak
  - ↓ Extracellular K+
  - ↓ RBC Deformability

Oxidative Injury

- ↓ NAD(P)H
- ↓ glutathione

1. Baseline Generation of Free Radicals
2. ↑ Free Radicals
3. ↑ Denatured Hemoglobin
4. ↓ NO Bioavailability
5. Hemolysis

RBC Membrane Injury

- ↑ RBC Membrane Microparticles
- ↑ RBC Aggregation
- ↑ RBC Adhesion

Perfusion

- ↓ Perfusion
- ↓ O₂ Delivery

In Critically Ill, POTENTIAL
- ↑ Risk of MOF and Death
Effects of Stored RBCs on Extracellular Solution

- ↑ Free Iron (hemolysis)
  - ↓ MAF
    - Immune Suppression
      - Infection
  - ↑ PS Expression
    - Hypercoagulation
  - Bioactive lipids
    - ↑ Inflammation
      - Capillary leak
        - ↓ Perfusion / ↓ O₂ Delivery
          - In Critically Ill, POTENTIAL ↑ Risk MOF / Death
  - Free Iron (Microparticles / Hemolysis)
    - ↓ NO Bio Availability
      - Altered Vasoregulation
Clinical Studies Examining Associations Of Red Cell Storage With Outcomes

- TRALI ¹
- Severe infection ²
- Decreased O₂ delivery ³,⁴
- Deep Vein Thrombosis¹¹
- MOF ⁵,¹⁴,¹⁵
- Mortality ⁶-¹³,¹⁶

¹ Silliman, C.C. J Lab Clin Med, 1994. 124(5)
² Offner PJ, Arch Surg 2002;137:711-71
³ Marik PE. JAMA. 1993; 269(23): 3024-29
⁸ Weinberg JA. J Trauma, 2007 63(2):480
¹⁰ Koch CG. NEJM 2008. 35812;1229-39
¹¹ Spinella PC. Critical Care. 2009
¹³ Edgren. Transfusion. 2010
¹⁴ Karam O. Critical Care. 2010
¹⁵ Gauvin F. Transfusion. 2010
¹⁶ Weinberg JA. J Trauma 2010
Some Studies Report No Difference Between Fresh And Old RBCs

- Ventilator Days $^1$-$^3$
- Hosp LOS $^2$, $^3$
- Splanchnic ischemia$^4$
- Mortality (cardiac surgery patients) $^5$
- Neurocognitive deficits $^6$
- Studies are **underpowered** to detect differences noted or are in **non-critically ill** populations

1. Vamvakas Transfusion 1999;39:701-710
5. Van Watering Transfusion 2006; 46:1712-1718
6. Weiskopf RB. Anesthesiology 2006;104(5):911-20
Clinical Efficacy

- Clinical trials in adults and children
  - ABLE
    - Adult ICU patients
  - RECESS
    - Adult Complex Cardiac Surgery
  - ARIPI
    - Premature infants
  - ABC-PICU
    - Critically ill children

- No Large Trials in Trauma

- Combat Casualties transfused very old RBCs
Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries

Philip C Spinella¹,², Christopher L Carroll¹, Ilene Staff³, Ronald Gross⁴, Jacqueline Mc Quay⁴, Lauren Keibel¹, Charles E Wade² and John B Holcomb⁵
Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital

Philip C. Spinella, MD; Jeremy G. Perkins, MD; Kurt W. Grathwohl, MD; Thomas Repine, MD; Alec C. Beekley, MD; James Sebesta, MD; Donald Jenkins, MD; Kenneth Azarow, MD; John B. Holcomb, MD; 31st Combat Support Hospital Research Working Group

Figure 1. Age of stored red blood cells (RBCs) on day of transfusion, n = 5,294 RBC units, mean storage age ± SD = 33 ± 6 days.
RBC Age in Combat Casualties

- At high risk of being transfused very old RBCs
- New RBC storage solution licensed out to 56 days **should not** be permitted to be transfused past 42 days
  - Less than 28 days would be optimal
  - ASBPO office plan is to use out to 56 days for inventory management
  - Combat casualties with shock and coagulopathy need RBCs with high efficacy and safety
  - 56 day old RBCs have reduced efficacy and safety compared to fresher RBCs
Summary

● Whole blood vs component studies need to be funded in trauma patients
  – Cold storage, low titer Group O and leukoreduction increase availability and safety

● Practitioners should not be influenced into not using whole blood

● Increased education and training for the appropriate and safe use of whole blood is needed
Summary

- Clinical Trials for platelets stored at 4C for 10 days vs 22C for 5 days in trauma patients are needed.
- In meantime whole blood derived platelets at 4C should be permitted at civilian trauma centers until apheresis platelets are licensed at 4C.
- Recently licensed RBCs to 56 days should not be permitted past 42 days for combat casualties.
- RBC storage age trials are required in massively bleeding trauma patients.
Summary

- Research for traumatic hemorrhagic shock also required for other causes of massive bleeding
  - GI
  - Obstetric
  - Intra-operative or post-operative
  - Sepsis
  - Pediatric
TRAUMA HEMOSTASIS AND OXYGENATION RESEARCH POSITION PAPER ON REMOTE DAMAGE CONTROL RESUSCITATION: DEFINITIONS, CURRENT PRACTICE, AND KNOWLEDGE GAPS


International multidisciplinary consensus on traumatic hemorrhagic shock resuscitation
Research Gaps

- Pre-hospital monitoring of shock and coagulopathy
- Hypotensive resuscitation for prolonged transports
- Endpoints of resuscitation
- Whole blood vs components
- Platelets at 4 vs 22C
- Lyophilized plasma and platelets
- Indications and safety of hemostatic adjuncts
- Goal directed hemostatic resuscitation vs empiric ratio based
- Efficacy and safety of pathogen reduction technology
- Efficacy and safety of plasma processing techniques
  - FFP vs. pooled solvent detergent treated plasma
- Role of TBI in hemorrhagic shock resuscitation
• **Influence of THOR**
  – Norwegian military and civilian incorporation of whole blood and platelets at 4C
  – Israeli incorporation of pre-hospital lyophilized plasma and plans for whole blood
  – Australian military change in policy regarding Group O whole blood
  – Rio de Janeiro, Brazil, development of whole blood based resuscitation capability
  – US civilian centers adopting pre-hospital plasma and whole blood transfusion capabilities
  – Multinational dissemination of whole blood collection and transfusion clinical practice guideline

• **THOR – NATO Alliance**
  – NATO Military Blood Advisory Team goal to begin having their official meetings at annual THOR RDCR Symposium
Current ongoing research projects
- Platelet function in leukoreduced whole blood
- Donor Performance for whole blood donors
- Tranexamic acid mechanisms and safety
  • All 3 awardees are THOR members
- RCT of Prehospital plasma
  • 2 awardees are THOR members

Research projects in development
- RCT of 4 vs 22C stored platelets
- RCT of group O whole blood
- RCT of RBC storage age in trauma patients
- RCT of FFP vs solvent detergent plasma in trauma
Questions?

Ask Me A Question

It's Free

Questions are guaranteed in life; Answers aren't.